CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

50-775

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

NDA 50-775
BIAXIN® XL Filmtab
(Clarithromycin Extended Release Tablets)

DATE of SUBMISSION
May. 03, 1999

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW

SPONSOR: Abbott Laboratories
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D-491, AP6B-1SW
Abbott Park, Illinois 60064-3500

REVIEWER: HE SUN, Ph.D.

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I. BACKGROUND

Clarithromycin (Abbott-56268) is a semi-synthetic macrolide antibiotic synthesized by [redacted] and developed and marketed by Abbott Laboratories. Clarithromycin has activity in vivo against *Staphylococcus spp., Streptococcus spp., Haemophilus spp., Moraxella catarrhalis,* and *Mycoplasma spp., Mycobacterium avium, Mycobacterium intracellulare,* and *Helicobacter pylori.* The in vitro activity of clarithromycin is generally greater than that of erythromycin, and clarithromycin is stable at lower pH (e.g., in the stomach) than erythromycin. A dose of clarithromycin gives higher circulating drug concentrations than an equivalent dose of erythromycin, and clarithromycin has a longer half-life than erythromycin. The activity of clarithromycin is enhanced by its extensive distribution into tissues and by the formation of a microbiologically active metabolite, 14(R)-hydroxy-clarithromycin (Abbott-62671). Immediate release clarithromycin tablets (250 mg and 500 mg) and granules for oral suspension (125 mg/5 mL and 250 mg/5 mL) are currently marketed in the United States under the trade name BIAXIN. Currently, immediate-release clarithromycin tablets are administered two or three times daily. For greater patient compliance and convenience, Abbott Laboratories has developed an extended-release tablet containing 500 mg clarithromycin for administration once daily.

Clarithromycin is an antibiotic drug which has been approved under NDAs for immediate release tablets (NDA 50-662) and granules for suspension (NDA 50-698). Development of this NDA was discussed with FDA.

This submission consists of 97 volumes.

II. SYNOPSIS:

Clarithromycin extended release (ER) tablet provides extended absorption from the GI tract after oral administration. Relative to a total daily dose of IR clarithromycin tablets, clarithromycin ER tablets provide lower and later steady-state peak plasma concentrations, but equivalent 24 hour AUC for both clarithromycin and its microbiologically active metabolite, 14(R)-hydroxy-clarithromycin. While the extent of the formation of the metabolites following the administration of ER tablets (2x500mg once daily) is not affected by food, administration under fasting conditions is associated with an approximately 30% lower clarithromycin AUC relative to the administration with food. Therefore, it is recommended that the ER formulation to be given with food.

III. RECOMMENDATION:

Overall, the submission is acceptable to the Division of Clinical Pharmacology and Biopharmaceutics. Labeling modifications are marked on the latest copy of sponsor's labeling. Please convey specific comments #5 (Dissolution Specification) to the sponsor.

IV. SPECIFIC COMMENTS:

1. For either 500mg or 1000mg daily dose, at steady-state under nonfasting conditions, AUC of clarithromycin and 14(R)-hydroxy-clarithromycin in the new ER3 formulation is equivalent

to that of IR. It is reported that AUC is an important pharmacodynamic parameter for clarithromycin activity.

2. For either 500mg or 1000mg daily dose, at steady-state under nonfasting conditions, Cmax of clarithromycin in ER formulation is about 35% lower than that of IR, while Cmax of 14(R)-hydroxy-clarithromycin is similar to that of IR. However, Cmax values are always greater than MICs of individual indications.

3. Cmin values of clarithromycin are 1 ug/ml for 1000mg dose and 0.5 ug/ml for 500 mg dose. MICs are considered to be in the [redacted] ug/ml range.

4. Food increases ER clarithromycin Cmax and AUC by 41% and 30%, respectively. Food has no effect on 14(R)-hydroxy-clarithromycin Cmax, Cmin, and AUC. The new ER formulation should be administered with food. Labeling language should be modified accordingly.

5. The dissolution specification should be revised as below (to be conveyed to sponsor)

[redacted]

/S/ 2/3/2000

He Sun, Ph.D.
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Frank Pelsor, Pharm. D. /S/ 3/3/2000
cc: NDA 50-755, HFD-520 (Clinical, CSO), HFD-340 (Viswanathan), HFD-880 (Pelsor, Sun), HFD-880 Div. File NDA.

V. STUDY SUMMARIES

V.1. Clarithromycin Formulation Development

V.1.a. Pilot Formulations

[redacted]

Reviewer's note:

These studies have good reference value, but have no significant impact on the final decision of the acceptance of the submission. Therefore they are listed at the end of the review (attachment B) for future reference only.

V.2. Final Tablet Formulation and Definitive Bioavailability Studies

[redacted]

- **STUDY M97-734**

Review question: At steady-state under nonfasting conditions, is the new ER formulation (dosed at 1000 mg/daily) equivalent to the IR formulation with respect to AUC for clarithromycin and 14(R)-hydroxy-clarithromycin ?

Review conclusion: All three lots of the test ER formulations are equivalent to IR formulation in AUC for both clarithromycin and 14(R)-hydroxy-clarithromycin. ER Clarithromycin Cmax decreased about 35% while ER 14(R)-hydroxy-clarithromycin is similar to that of IR.

Additional review comments: It is reported that the anti-infective activity of clarithromycin is more related to AUC values for the labeled indications. Cmin of ER clarithromycin and 14(R)-hydroxy-clarithromycin are all greater than MICs for labeled indications.

Thirty healthy adult subjects (24 males, 6 females) completed all phases of a study designed to compare the multiple-dose pharmacokinetics under nonfasting conditions of three lots of an extended-release clarithromycin tablet formulation with those of the immediate-release tablet formulation. The study was conducted according to an open-label, four-period,

randomized crossover design. The clarithromycin dosage forms included three lots of an ER tablet formulation, designated ER1, ER2 and ER3, each of which contained 500 mg clarithromycin and 20% of the release-controlling polymer. Each lot was manufactured to a different granulation endpoint. These test formulations were administered as 1000 mg doses (two tablets) once daily for five days with food. The reference IR tablets also contained 500 mg clarithromycin and were administered as 500 mg doses (one tablet) every 12 hours for five days with food. The breakfast served on Day 5 provided approximately [redacted] with approximately 20% of the calories from fat. Blood samples were collected for 24 hours after the morning dose on Day 5. Washout periods of at least one week separated the last dose in a period from the first dose in any following period.

[redacted] Mean steady-state clarithromycin plasma concentration-time profiles for the four regimens examined in this study are shown in Figure 5. Pharmacokinetic parameters were calculated for clarithromycin and 14(R)-hydroxy-clarithromycin using standard noncompartmental methods. Summaries (mean ± SD) of the pharmacokinetic results after multiple dosing are presented in the following tables.

Clarithromycin

Regimen	N	Cmax (mcg/mL)	Tmax (h)	Cmin (mcg/mL)	AUC (mcg-h/mL)	DFL#
ER1	30	2.81 ± 1.04*	6.5 ± 4.0*	0.83 ± 0.34	42.2 ± 12.8	[redacted]
ER2	30	2.78 ± 0.96*	5.5 ± 3.5*	0.83 ± 0.44	44.9 ± 15.3	
ER3	30	2.59 ± 0.71*	7.8 ± 4.0*	0.76 ± 0.37*	42.1 ± 13.2*	
IR-reference	30	3.51 ± 0.98	2.1 ± 0.6	0.91 ± 0.39	46.1 ± 13.8	

* Statistically significantly different from the reference IR tablet regimen
# DFL – Degree of fluctuation

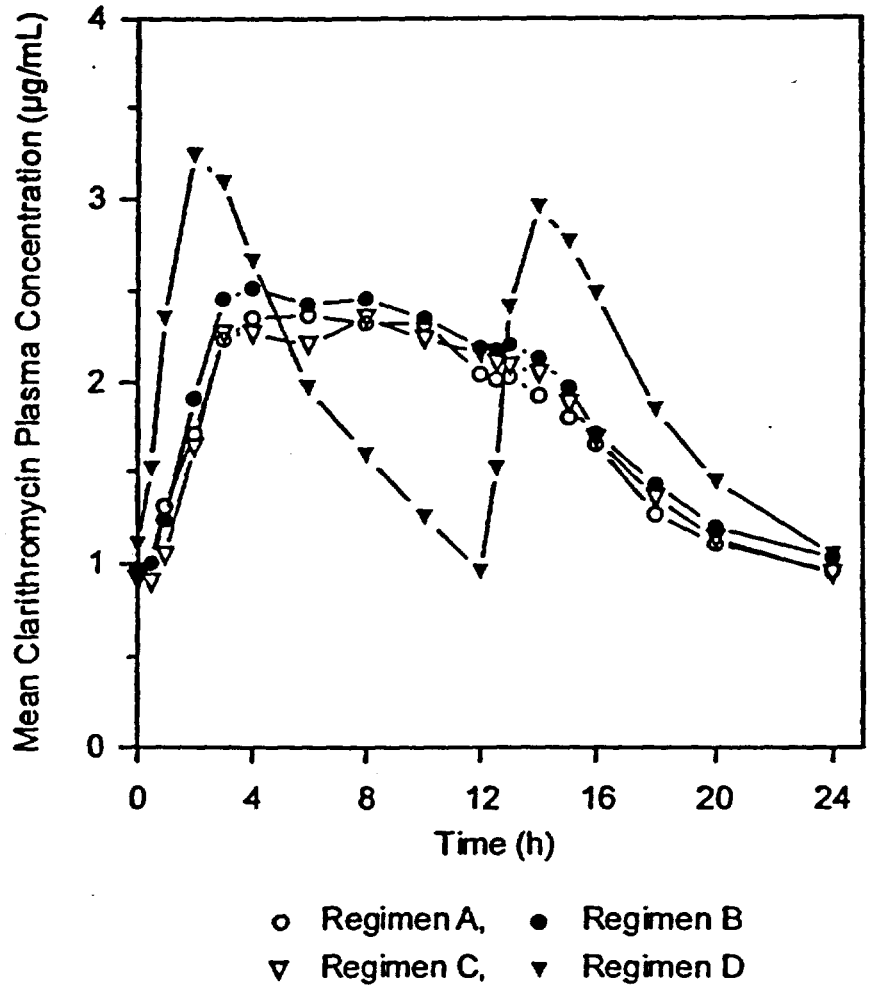
14(R)-Hydroxy-Clarithromycin

Regimen	N	Cmax (mcg/mL)	Tmax (h)	Cmin (mcg/mL)	AUC (mcg-h/mL)	DFL#
ER1	30	0.86 ± 0.28	6.9 ± 4.1*	0.46 ± 0.13	15.3 ± 3.6	[redacted]
ER2	30	0.82 ± 0.20	6.5 ± 5.0*	0.45 ± 0.14	15.6 ± 3.5*	
ER3	30	0.79 ± 0.17	8.7 ± 5.2*	0.42 ± 0.13	15.1 ± 3.2	
IR-reference	30	0.82 ± 0.16	2.4 ± 1.7	0.42 ± 0.10	14.4 ± 2.9	

* Statistically significantly different from the reference IR tablet regimen
# DFL – Degree of fluctuation

Point estimates of relative bioavailability and 90% confidence intervals for the two one-sided tests procedure from analysis of AUC are presented in the following table.

Figure 8. Mean Steady-State Clarithromycin Plasma Concentration-Time Profiles for Study M97-734



Analyte	N	Relative Bioavailability: Formulation Comparison	Point Estimate	90% CI Interval
Clarithromycin	30	ER1 vs. IR	0.921	0.854 - 0.994
14(R)-Hydroxy-Clarithromycin	30	ER1 vs. IR	1.058	1.001 - 1.119
Clarithromycin	30	ER2 vs. IR	0.962	0.891 - 1.038
14(R)-Hydroxy-Clarithromycin	30	ER2 vs. IR	1.078	1.020 - 1.139
Clarithromycin	30	ER3 vs. IR	0.903	0.837 - 0.975
14(R)-Hydroxy-Clarithromycin	30	ER3 vs. IR	1.041	0.984 - 1.100

Conclusion: At steady-state under nonfasting conditions, all three lots of the test extended-release formulation met the requirements for demonstrating equivalence (90% confidence interval between 0.80 and 1.25) with respect to AUC for clarithromycin and 14(R)-hydroxy-clarithromycin. The significantly lower clarithromycin Cmax values and the later Tmax values suggested that all three lots of the test formulation provided extended release of clarithromycin in vivo. The significantly lower DFLs (degree of fluctuations) indicated that clarithromycin plasma concentrations fluctuated less for the extended-release tablet regimens than for the immediate-release tablet regimen.

- **STUDY M97-814**

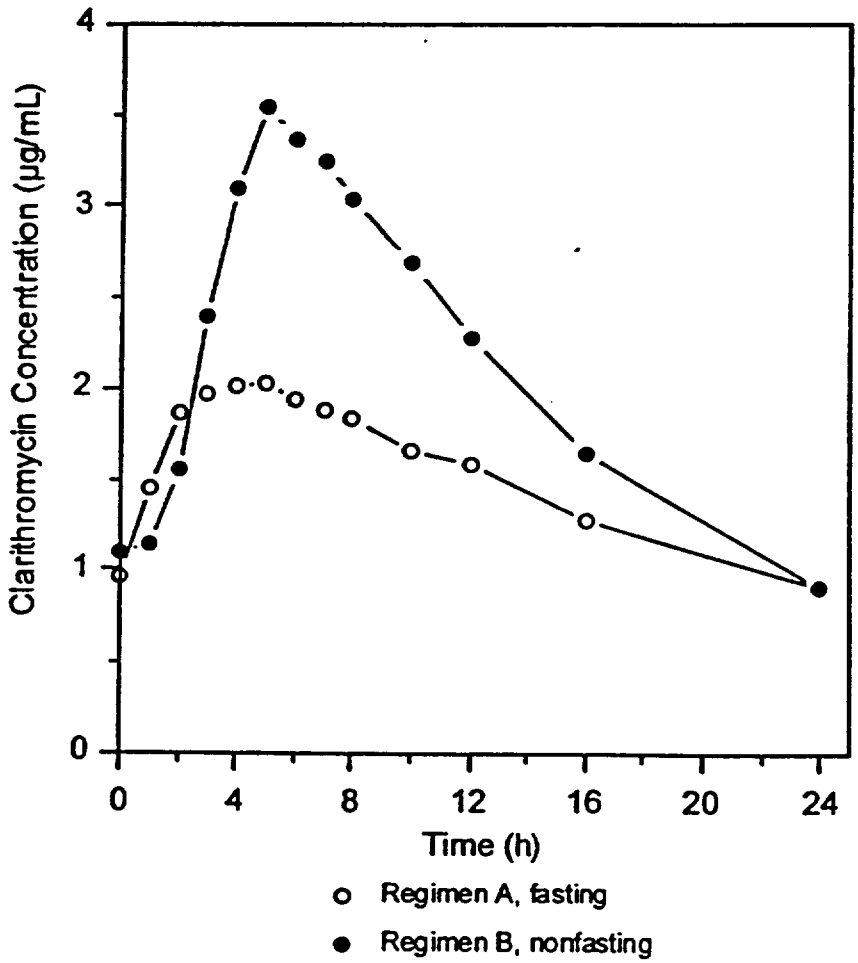
Review question: What is the effect of food on the bioavailability of the new ER formulation at 2x500 mg dose?

Review conclusion: Food increases clarithromycin Cmax and AUC of ER by 41 % and 30%, respectively. Food has no effect on 14(R)-hydroxy-clarithromycin Cmax, Cmin, and AUC.

Thirty-two healthy adult subjects (22 males, 10 females) completed all phases of a study designed to determine the effect of food on the bioavailability of a clarithromycin ER formulation at steady-state. The study was conducted according to an open-label, two-period, randomized crossover design. The clarithromycin dosage form was an ER tablet formulation which contained 500 mg clarithromycin and 20% of the release-controlling polymer. The formulation was administered as 1000 mg doses (two 500 mg tablets) once daily for five days. For the fasting regimen, the subjects took each dose of clarithromycin following an 8-hour fast. For the nonfasting regimen, the subjects took each dose of clarithromycin 30 minutes after starting breakfast. The breakfast served on Day 5 provided [redacted] with 50.4% of the calories from fat. Blood samples were collected for 24 hours after the morning dose on Day 5. A washout period of nine days separated the last dose of the first period from the first dose of the second period.

[redacted] Mean clarithromycin plasma concentration-time profiles for the two regimens examined in this study are shown in Figure 6. Pharmacokinetic parameters were calculated for clarithromycin and 14(R)-hydroxy-clarithromycin using standard noncompartmental methods. Summaries (mean ± SD) of the pharmacokinetic results after multiple dosing are presented in the following tables.

Figure 3. Mean Steady-State Clarithromycin Plasma Concentration-Time Profiles for Study M97-814



Clarithromycin

Regimen	N	Cmax (mcg/mL)	Tmax (h)	Cmin (mcg/mL)	AUC (mcg-h/mL)	DFL
Fasting	32	2.33 ± 0.70*	5.5 ± 3.1	0.76 ± 0.44	35.9 ± 12.4*	
Nonfasting	32	3.91 ± 1.04	5.6 ± 2.0	0.80 ± 0.38	49.2 ± 10.5	

* Statistically significantly different from Regimen B (nonfasting regimen)

14(R)-Hydroxy-Clarithromycin

Regimen	N	Cmax (mcg/mL)	Tmax (h)	Cmin (mcg/ml)	AUC (mcg-h/mL)	DFL
Fasting	32	0.85 ± 0.27	4.9 ± 4.2	0.40 ± 0.17	14.2 ± 3.7	
Nonfasting	32	0.85 ± 0.20	6.0 ± 4.0	0.39 ± 0.12	14.6 ± 3.1	

The fasting regimen was compared to the nonfasting regimen using two one-sided tests procedure with 90% confidence intervals. The 90% confidence intervals for clarithromycin Cmax and AUC did not fall within the ranges established to show equivalence of the fasting and nonfasting regimens [redacted] Point estimates are presented.

Relative Bioavailability

Analyte	N	Formulation Comparison	Relative Bioavailability Point Estimate	% Change
Cmax	32	Fasting vs. Nonfasting	0.587	- 41%
AUC	32	Fasting vs. Nonfasting	0.701	- 30%
Cmin	32	Fasting vs. Nonfasting	0.959	- 4%

14(R)-Hydroxy-Clarithromycin

Analyte	N	Formulation Comparison	Relative Bioavailability Point Estimate	90% CI Range
Cmax	32	Fasting vs. Nonfasting	0.974	0.884 - 1.074
AUC	32	Fasting vs. Nonfasting	0.959	0.884 - 1.041
Cmin	32	Fasting vs. Nonfasting	1.017	0.864 - 1.188

The clarithromycin Cmax and AUC central values for the extended-release clarithromycin tablet formulation administered under fasting conditions were approximately 41 % and 30% lower, respectively, than the central values for the same formulation administered with food. The clarithromycin Cmin values and the 14(R)-hydroxy-clarithromycin Cmax, Cmin, and AUC were similar when the extended-release formulation was given under fasting and nonfasting conditions.

- **STUDY M98-976**

Review question: At steady-state under nonfasting conditions, is the new ER formulation (dosed at 500 mg/daily) equivalent to the IR formulation with respect to AUC for clarithromycin and 14(R)-hydroxy-clarithromycin ?

Review conclusion: The test ER formulation is equivalent to IR formulation in AUC for both clarithromycin and 14(R)-hydroxy-clarithromycin. ER Clarithromycin Cmax decreased about 35% while ER 14(R)-hydroxy-clarithromycin is similar to that of IR.

Thirty-two healthy adult subjects (17 males, 15 females) completed both phases of a study designed to compare the multiple-dose pharmacokinetics under nonfasting conditions of an extended-release clarithromycin tablet formulation with those of the immediate-release tablet formulation at a total daily dose of 500 mg. The study was conducted according to an open-label, two-period, randomized, crossover design. The clarithromycin dosage forms included an ER tablet formulation which contained 500 mg clarithromycin and 20% of the release-controlling polymer. The lot used in the study was one of three lots, designated ER3, that were examined in the previous study (total daily dose of 1000 mg). The test ER formulation was administered as 500 mg (one tablet) once daily for five days with food. The reference IR tablets contained 250 mg clarithromycin and were administered as 250 mg (one tablet) every 12 hours for five days with food. The breakfast served on Day 5 provided approximately [redacted] with approximately 20% of the calories from fat. Blood samples were collected for 24 hours after the morning dose on Day 5. A washout interval of one week separated the last dose in Period 1 from the first dose in Period 2.

[redacted] Mean steady-state clarithromycin plasma concentration-time profiles for the two regimens examined in this study are shown in Figure 7. Pharmacokinetic parameters were calculated for clarithromycin and 14(R)-hydroxy-clarithromycin using standard noncompartmental methods. Summaries (mean ± SD) of the pharmacokinetic results after multiple dosing are presented in the following tables.

Clarithromycin

Regimen	N	Cmax (mcg/mL)	Tmax (h)	Cmin (mcg/mL)	AUC (mcg-h/mL)	DFL
A	32	1.45 ± 0.43*	5.6 ± 2.1*	0.31 ± 0.23*	20.4 ± 8.7	[redacted]
B	32	1.94 ± 0.68	2.4 ± 1.4	0.34 ± 0.15	21.0 ± 6.9	

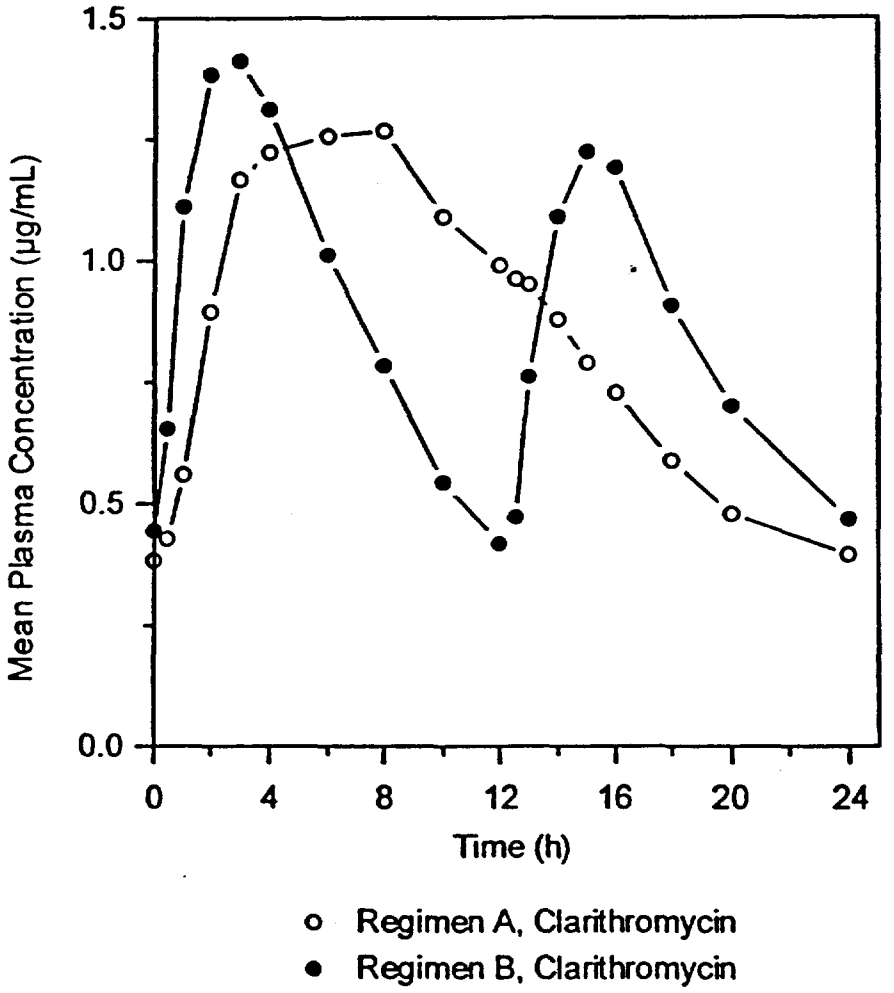
* Statistically significantly different from Regimen B (reference, immediate-release tablet regimen)

14(R)-Hydroxy-Clarithromycin

Regimen	N	Cmax (mcg/mL)	Tmax (h)	Cmin (mcg/mL)	AUC (mcg-h/mL)	DFL
A	32	0.58 ± 0.17	6.0 ± 2.3*	0.23 ± 0.13	9.5 ± 3.5	[redacted]
B	32	0.60 ± 0.15	3.0 ± 2.3	0.24 ± 0.10	9.6 ± 2.8	

* Statistically significantly different from Regimen B (reference, immediate-release tablet regimen)

Figure 3. Mean Steady-State Clarithromycin Plasma Concentration-Time Profiles for Study M98-976



Point estimates of relative bioavailability and 90% confidence intervals for the two one-sided tests procedure from analysis of AUC are presented in the following table.

			Relative Bioavailability	
Analyte	N	Formulation Comparison	Point Estimate	90% CI Interval
Clarithromycin	32	A vs. B	0.946	0.848 - 1.055
14(R)-Hydroxy-Clarithromycin	32	A vs. B	0.969	0.890 - 1.056

At steady-state under nonfasting conditions, the test extended-release formulation met the requirements for demonstrating equivalence (90% confidence interval between 0.80 and 1.25) with respect to AUC for clarithromycin and 14(R)-hydroxy-clarithromycin. The significantly lower clarithromycin Cmax values and later Tmax values suggested that the test formulation provided extended release of clarithromycin in vivo. The significantly lower DFLs indicated that clarithromycin plasma concentrations fluctuated less for the extended-release tablet regimens than for the immediate release tablet regimen.

Final integration of all study results:

1. For either 500mg or 1000mg daily dose, at steady-state under nonfasting conditions, AUC of clarithromycin and 14(R)-hydroxy-clarithromycin in the new ER formulation is equivalence to that of IR,

2. For either 500mg or 1000mg daily dose, at steady-state under nonfasting conditions, Cmax of clarithromycin in ER formulation is about 35% lower than that of IR, while Cmax of 14(R)-hydroxy-clarithromycin is similar to that of IR.

3. Cmin of clarithromycin is 1 ug/ml for 1000mg dose and 0.5 ug/ml for 500 mg dose.

4. Food increases clarithromycin Cmax and AUC of ER by 41 % and 30%, respectively. Food has no effect on 14(R)-hydroxy-clarithromycin Cmax, Cmin, and AUC.

5. The new ER formulation is acceptable and the ER drug product should be given with food.

- **DISSOLUTION TEST.**

The drug release testing method used for ER formulation is:

Mean release data for clarithromycin ER 500 mg tablets are presented in Table next page.

7 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

VII. ATTACHMENT B: BIOPHARMACEUTICAL STUDIES FOR PILOT FORMULATIONS DURING FORMULATION DEVELOPMENT:

- **STUDY M96-465**

Study question: what will be the best percentage of release-controlling polymer in the to be developed ER formulations ?

Study condition: 500mg single dose with food.

Sponsor's choice: 20%

Twenty-three healthy subjects (12 males, 11 females) completed this pilot bioavailability study in which they received four single 500 mg doses of clarithromycin with food according to an open-label, four-period, randomized crossover design. The clarithromycin dosage forms included three test 500 mg ER tablet formulations which contained 10%, 20%, or 30% of the release-controlling polymer, and a reference, 500 mg IR tablet. Blood samples were collected for 48 hours after each dose. Washout periods of one wee separated the doses.

Mean clarithromycin plasma concentration-time profiles for the four formulations examined in this study are shown in Figure 1. Pharmacokinetic parameters were calculated for clarithromycin and 14(R)-hydroxy-clarithromycin using standard noncompartmental methods. Summaries (mean ± SD) of the pharmacokinetic results are presented in the following tables.

Clarithromycin

Formulation	N	Cmax (mcg/mL)	Tmax (h)	AUC+ (mcg-h/mL)	t1/2 (h)
ER-10%	23	1.33 ± 0.70*	5.5 ± 2.4*	15.1 ± 6.5*	5.6
ER-20%	23	1.19 ± 0.60*	5.0 ± 1.7*	15.0 ± 6.5*	6.1
ER-30%	23	1.01 ± 0.48*	5.5 ± 2.2*	14.8 ± 7.5*	6.0
IR-Reference	23	2.57 ± 0.70	2.2 ± 0.5	17.7 ± 5.6	4.4

14(R)-Hydroxy-Clarithromycin

Formulation	N	Cmax (mcg/mL)	Tmax (h)	AUC (mcg-h/mL)	t1/2 (h)
ER-10%	23	0.55 ± 0.23*	5.9 ± 1.8*	9.4 ± 2.8	9.3
ER-20%	23	0.53 ± 0.18*	6.0 ± 2.3*	9.6 ± 2.7	9.2
ER-30%	23	0.49 ± 0.16*	7.2 ± 6.4*	9.3 ± 2.7	8.9
IR-Reference	23	0.79 ± 0.23	3.2 ± 2.1	10.1 ± 2.4	7.8

+ N=22; data for Subject 107 did not allow estimation of half-life or extrapolation of AUC to infinite time.

* Statistically significantly different from the IR reference tablet

** Elimination rate constant significantly different from the IR reference tablet

Figure 4. Mean Clarithromycin Plasma Concentration-Time Profiles for Study M96-465

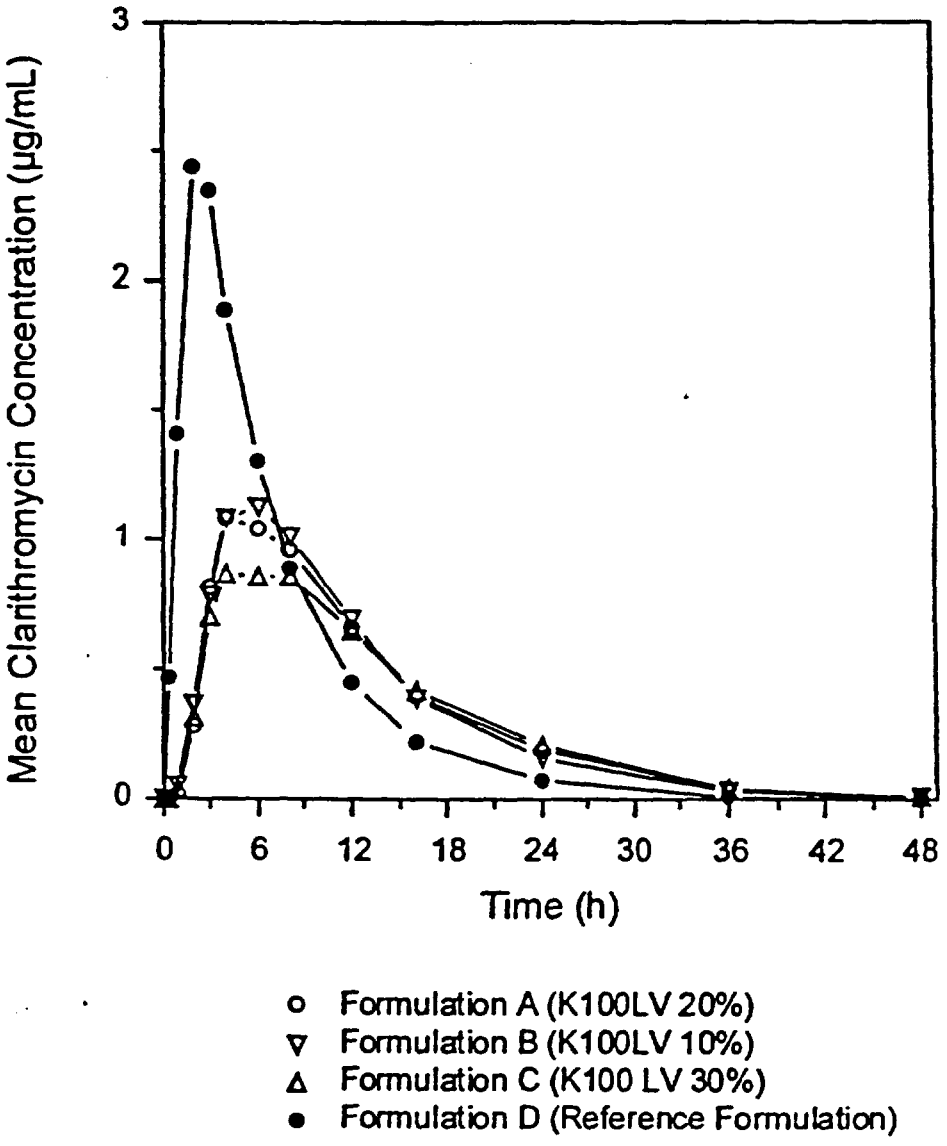
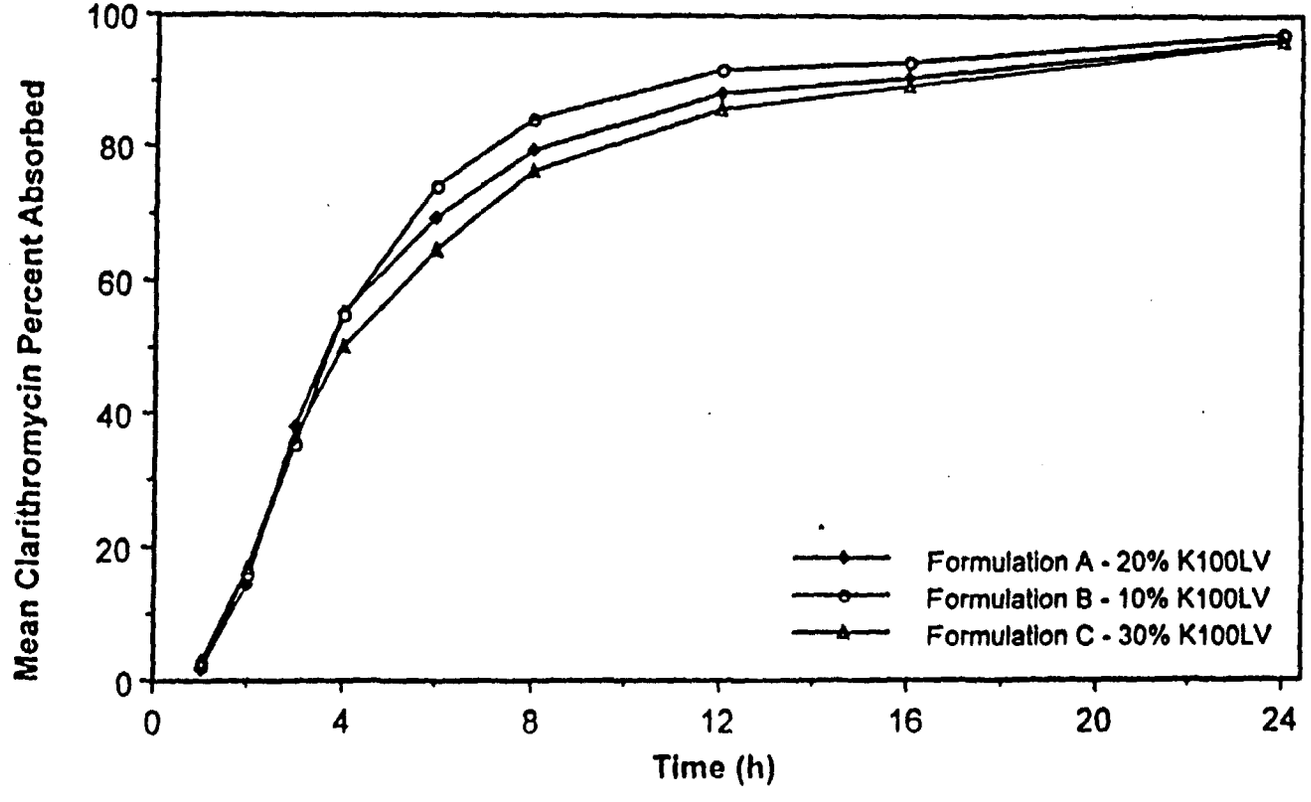


Figure 5. Mean Clarithromycin Absorption vs. Time Profiles for Formulations A, B, and C in Study M96-465



2 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

- **STUDY M96-454**

Study question: what will be the best percentage of release-controlling polymer in the to be developed ER formulations ?

Study condition: 1000mg multiple dose

Sponsor's choice: 20%

In this pilot bioavailability study, 22 healthy adult subjects (18 males, 4 females) provided evaluable pharmacokinetic data for three single- and multiple-dose regimens of clarithromycin according to an open-label, three-period, randomized crossover design. The clarithromycin dosage forms included 500 mg ER tablet formulations which contained 10% or 20% of the release-controlling polymer and a reference 500 mg IR tablet. The test formulations were administered as 1000 mg doses (two 500 mg tablets). A single 1000 mg dose was administered on Day 1, and a multiple-dose regimen of 1000 mg once daily for three days was started on Day 3. For the reference formulation, a single 500 mg dose was administered on Day 1, and a multiple dose regimen of 500mg every 12 hours for three days was started on Day 3. All doses were administered with food. Blood samples were collected for 48 hours after the morning dose on Day 5 (third day of the multiple-dose regimen). Washout periods of at least one week separated the last dose in a period from the first dose in any following period.

Mean Day 5 clarithromycin plasma concentration-time profiles for the three regimens examined in this study are shown in Figure 4. Pharmacokinetic parameters were calculated for clarithromycin and 14(R)-hydroxy-clarithromycin using standard noncompartmental methods. Summaries (mean ± SD) of the pharmacokinetic results after multiple dosing are presented in the following tables.

Clarithromycin - Day 5

Regirrien	N	Cmax (mcg/mL)	Tmax (h)	Cmin (mcg/mL)	AUC (mcg-h/mL)
ER-10%	22	2.66 ± 0.87*	6.9 ± 3.3*	0.67 ± 0.39	40.2 ± 13.8
ER-20%	22	2.45 ± 0.69*	8.6 ± 4.4*	0.70 ± 0.37	39.6 ± 12.8
IR reference	22	3.21 ± 0.78	1.9 ± 0.6	0.78 ± 0.29	40.8 ± 11.8

DFL

*Statistically significantly different from the IR reference tablet regimen
+Statistically significantly different from ER- 10% regimen

14(R)-Hydroxy- Clarithromycin - Day 5

Regimen	N	Cmax (mcg/mL)	Tmax (h)	Cmin (mcg/mL)	AUC (mcg-h/mL)	DFL
ER-10%	22	0.82 ± 0.23	7.8 ± 3.3*	0.41 ± 0.16	15.0 ± 4.6	
ER-20%	22	0.81 ± 0.19	6.8 ± 4.2*	0.42 ± 0.19	15.2 ± 4.4	
IR reference	22	0.82 ± 0.21	2.0 ± 0.8	0.42 ± 0.13	14.4 ± 3.9	

* Statistically significantly different from the IR reference tablet regimen

Point estimates of relative bioavailability and 90% confidence intervals for the two one-sided tests procedure from analysis of Day 5 AUC are presented in the following table.

Analyte		Formulation Comparison	Relative Bioavailability Point Estimate	90% CI Interval
Clarithromycin	22	ER- 10% vs. IR	0.970	0.899 - 1.046
14(R)-Hydroxy-Clarithromycin	22	ER- 10% vs. IR	1.043	0.964 - 1.123
Clarithromycin	22	ER-20% vs. IR	0.964	0.893 - 1.039
14(R)-Hydroxy-Clarithromycin	22	ER-20% vs. IR	1.059	0.980 - 1.142

At steady-state under nonfasting conditions, both of the extended-release formulations met the requirements for equivalence (90% confidence intervals between 0.80 to 1.25) with respect to AUC for clarithromycin and 14(R)hydroxy-clarithromycin. The significantly lower Cmax values and the later Tmax values suggested that both test formulations provided extended release of clarithromycin in vivo. The significantly lower DFLs indicated that plasma concentrations fluctuated less for the extended-release tablet regimens than for the immediate-release tablet regimen. The significantly lower fluctuation index for Regimen A compared to Regimen B contributed to the decision to continue development of the 20% polymer tablet rather than the 10% polymer tablet.

Figure 6. Mean Day 5 Clarithromycin Plasma Concentration-Time Profiles for Study M96-454